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(54) Vitamin, betacarotene and zinc composition for sperm health

(57) A formulation for sperm health comprises vitamin E, vitamin C, zinc and betacarotene. The components together act in synergy to exert numerous beneficial effects on sperm motility, maturation, flexibility of sperm tails and reduced sperm clumping. The formulation can be used as a food supplement or can be administered to male subjects in tablet form.

The preferred formulation contains 250mg of vitamin C, 15mg of betacarotene, 100mg of vitamin E and 10mg of zinc gluconate in conjunction with binding and flavouring agents.

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The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1995

COMPOSITION FOR SPERM HEALTH

This invention relates to a composition which may suitably be taken as a food supplement, and to its use for improving sperm health.

Over the last 50 years, the average sperm count has virtually halved from 113 million sperm per ml to 66 million per ml (Carlsen E. et al. (1992) BMJ 305: 609-612). Semen volume has dropped from an average of 3.4ml to 2.75ml; sperm motility has decreased and the percentage of sperm with abnormal architecture has increased.

It is estimated that as many as 10% of sperm can be abnormal without loss of fertility. It is now considered usual, however, to find up to 40% of sperm in the ejaculate with architectural abnormalities. It takes an average of 74 days for the production of a mature sperm from its primitive germ cell, and then a further 20 days for the sperm to traverse the epididymis, during which time they gain their motility. After this, sperm are in the vas deferens for at least another six days before ejaculation. During this 100 day time period, each sperm can undergo irreparable damage.

Most men have 20% to 40% obviously abnormal sperm when semen is examined in the laboratory. Many more have genetic abnormalities that remain undetected. It is estimated that 40% of all sperm damage is due to the harmful effects of free radicals.

Oxidative damage to DNA can result in the wrong nucleotide bases being inserted when the DNA sequence is read. If this occurs in a dividing germ cell destined to produce a sperm, a mutation results which may cause sub-fertility, birth defects, genetic diseases or childhood cancers in resultant offspring.

It is known that certain vitamins and minerals, if administered individually to male subjects, improve sperm quality and quantity.

For example, the use of vitamin C has been shown to play a role in protecting sperm. Vitamin C is actively secreted into semen and is present at concentrations eight times higher than those found in the blood. It has been shown that if between 250mg and 1000mg vitamin C is given to males, sperm quality is significantly improved as vitamin C, by acting as an anti-oxidant, decreases sperm agglutination and decreases free radical attack.

In one study, 35 infertile men were given 500mg of vitamin C every twelve hours (i.e. twice a day) for one month. After only one week, the average percentage of sperm clumped together had dropped from 37% to 14%. After two weeks, sperm agglutination had dropped to 13% and at four weeks was down to 11%. A significant improvement in the overall quality of the men's sperm was observed, including the percentage of normal sperm present, sperm viability and sperm motility.

Research also shows that vitamin C protects the genetic material (DNA) of sperm against the oxidising reactions of free radicals. This reduces the risk of siring offspring with an inherited genetic disease.

The UK recommended reference nutrient intake of vitamin C is currently 40mg/day, based on the amount needed to protect against vitamin C deficiency disease (scurvy) and to maintain healthy tissues.

It has also been shown that vitamin E, when administered per se, improves sperm quality. Unlike vitamin

C, it is fat-soluble, which means it can penetrate cell membranes and body fats to protect them against oxidising free radical attacks.

The reference nutrient intake for vitamin E is 10mg/day. This is based on providing enough vitamin E to prevent oxidation of polyunsaturated fats in our diet. However, fifty per cent of British men obtain less than 9.3mg per day.

Zinc is also known to have a role in sperm health, as it is essential for spermatogenesis. Zinc deficiency is known to cause low sperm count; low testosterone levels and male infertility. It also reduces male libido, and is associated with impotence.

Zinc plays a major role in sensitivity of tissues to sex hormones and zinc deficiency in men results in delayed puberty. Eighteen to twenty year old males who are zinc deficient remain prepubertal.

The new European recommended daily intake of zinc is 15mg per day, but 50% of British men obtain less than 10.9mg zinc per day.

However, with the present falling sperm count and the increase in the number of abnormal sperm, there is a need to find a way to promote sperm health more effectively.

We have now made the unexpected finding that a formulation comprising a combination of active ingredients acts synergistically, and is very beneficial to sperm health.

According to the present invention there is provided a formulation for sperm health comprising vitamin E, vitamin C, zinc and betacarotene. Such a formulation could be suitably taken as a food supplement.

Preferably, the formulation comprises 50-200mg of vitamin E, 150-1000mg vitamin C, 5-20mg zinc and 7.5-20mg betacarotene.

Most preferably, the formulation comprises about

100mg vitamin E, 250mg vitamin C, 10mg zinc and 15 mg betacarotene.

Desirably, the formulation further comprises at least one binder and/or at least one flavour agent. The formulation could then be suitably taken by male subjects in tablet form as a food supplement. Examples of suitable binders are microcrystallic cellulose and magnesium stearate, and examples of suitable flavour agents are stearic acid and silica.

The present invention also provides the above-described formulation or a pharmaceutical preparation thereof for use in medicine.

Although the formulation is preferably for use as a food supplement, it is also envisaged that the formulation could be administered to male subjects specifically for medical purposes for the improvement of sperm health and maintenance of sperm count levels.

By using this particular combination of antioxidants, it has been found that there is a significant synergistic effect.

In accordance with the present invention, it has been found that by using vitamin C and vitamin E together in a single formulation, the vitamin C regenerates vitamin E from its oxidised form into its reduced one, after the vitamin E has mopped up a superoxide free radical. Further, by combining betacarotene and zinc with vitamin C, their respective antioxidant effects free up more vitamin C to regenerate and protect vitamin E, thus keeping more of a substance called non-specific sperm agglutinin (NSSA) in its reduced form. NSSA is a seminal protein that binds to sperm and plays an important role in sperm clumping.

Vitamin E is a component of the non-specific sperm agglutinin. NSSA is made up of a protein, a sugar, vitamin E and several sulphur-containing groups.

NSSA exists in either an oxidised or a reduced form. When in the reduced form, it binds to sperm heads

through its sulfhydryl groups, and prevents sperm clumping together. This increases sperm motility.

When NSSA exists in its oxidised form, it cannot bind to sperm, and sperm therefore stick to each other. This causes them to clump together and become immobile, and if 20% or more sperm are affected, this leads to infertility.

It has been discovered that the use of a combination of active ingredients can prevent oxidation and keep the NSSA in a reduced form, which will improve sperm quality by decreasing clumping, and also such a formulation will mop up free radicals and decrease oxidation levels.

High levels of superoxide radicals in semen are linked with subfertility. Vitamin E will mop up these superoxide radicals and improve fertility. Also, vitamin E plays an important role in preventing sperm clumping and promoting motility. Vitamin E, as a fat-soluble antioxidant, also has an additional, beneficial effect on sperm motility as it improves sperm cell wall flexibility. One of the benefits of the formulation of the present invention is that NSSA and vitamin E itself are maintained in a non-oxidised form by vitamin C. By acting as an anti-oxidant, vitamin C keeps the agglutinin in its reduced form so that it can bind to sperm and regenerates vitamin E.

It has also been found that betacarotene can be used effectively to assist vitamins E, C and zinc as an antioxidant to improve sperm health. As betacarotene is a water-soluble vitamin, it may protect sperm in semen from free radical attack in a similar way to vitamin C.

Further, it is believed that betacarotene may have a beneficial effect on sperm in its own right.

Vitamin A is thought to be important in sperm maturation whilst the sperm travels through the epididymis and beyond. Sperm vitamin A may also be important for the egg upon fertilisation.

Betacarotene is converted into vitamin A when body

levels are low. Thus, the betacarotene acts both as a powerful antioxidant and, when necessary, is converted into vitamin A to assist sperm maturation.

Zinc is also an antioxidant and has likewise been found to act in synergy with vitamins C, E and betacarotene.

Increases in extracellular zinc cause corresponding increases in spermatozoal zinc, which inhibit sperm oxygen consumption by slowing sperm down within the male tract and conserving their energy. It now seems that zinc is involved in maintaining sperm in a transitory quiescent state until they enter the female reproductive tract.

In the female tract, zinc levels are low and zinc is rapidly removed from sperm, causing a sudden spurt of motility. Thus, zinc both acts as an antioxidant in synergy with vitamins C, E and betacarotene, and preserves sperm energy until it is required.

Zinc also protects sperm DNA (chromatin) from degradation and has a significant effect on the secondary structure (2D-shape) of human sperm protamines - proteins that condense 85% of sperm DNA into an insoluble, stable, nucleoprotein complex.

This is thought to be physiologically significant considering the high levels of zinc found in human sperm. Sperm chromatin must be condensed for successful fertilisation.

This is another example of how zinc and antioxidant vitamins act synergistically to improve sperm health.

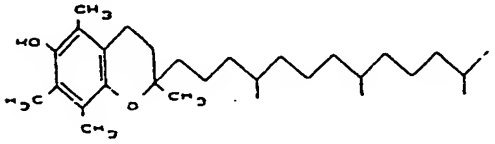
When a sperm meets an egg, it releases enzymes from a sac at the sperm head which digest the outer egg coating and allow sperm penetration. Sometimes, these enzymes are discharged early and spontaneously, which effectively renders a sperm no longer capable of fertilisation. Zinc has been shown to significantly reduce the number of sperm undergoing the acrosome reaction -

probably by altering membrane permeability to potassium.

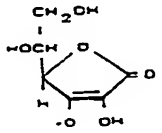
This effect is reversible, so when zinc concentrations are reduced in the female tract, the acrosome reaction can again occur. This mechanism reduces the change of a spontaneous acrosome reaction occurring before the sperm reaches the egg and fertilisation can take place.

Thus, it will be realised that, although the individual components of the formulation of the present invention would be expected to show some positive effect on sperm health by acting as individual antioxidants, the components together act in synergy to exert numerous other beneficial effects on: sperm motility (Vitamin E, zinc), DNA integrity (Vitamin C, zinc), chromatin condensed structure (zinc), sperm maturation (betacarotene), inhibition of the acrosome reaction (zinc), preservation of sperm energy stores (zinc), reducing sperm clumping (vitamin C and vitamin E) and improved flexibility of sperm tails (vitamin E), leading to improved motile efficiency.

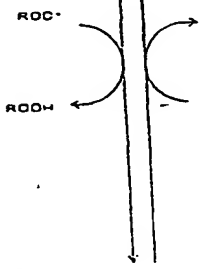
In addition, vitamin C is essential for the regeneration of vitamin E once it has exerted its antioxidant effect. The vitamin E radical is inactivated, and the active vitamin reformed, by reaction with vitamin C in accordance with the following reaction:

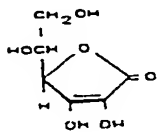


α-Tocopherol

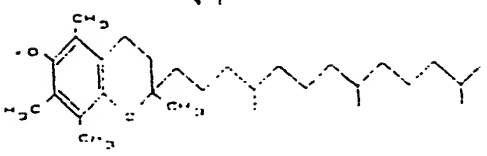


Semidehydro-ascorbate





Ascorbate



α-Tocopheroxyl radical

The synergistic effects of these ingredients on sperm health - especially in regard to NSSA function and the mopping up of free superoxide radicals - may help to reverse the observed downturn in sperm health.

In order to illustrate the present invention, the following example is given of a formulation in accordance with the present invention.

Example

Vitamin C	250mg	Active
Betacarotene	15mg	Active
Vitamin E	100mg	Active
Zinc Gluconate	10mg	Active
Microcrystallic Cellulose	180mg	Binder
Magnesium Stearate		Binder
Stearic Acid		Flavour Agent
Silica		Flavour Agent

CLAIMS:

1. A formulation for sperm health comprising vitamin E, vitamin C, zinc and betacarotene.

2. A formulation according to claim 1, which comprises 50-200mg vitamin E, 150-1000mg vitamin C, 5-20mg zinc and 7.5-20mg betacarotene.

3. A formulation according to claim 2, which comprises 100mg vitamin E, 250mg vitamin C, 10mg zinc and 15mg betacarotene.

4. A formulation according to claim 1, 2 or 3, which further comprises at least one binder and/or at least one flavour agent.

5. A formulation according to claim 4, wherein the binder is microcrystallic cellulose and/or magnesium stearate.

6. A formulation according to claim 4, wherein the flavour agent is stearic acid and/or silica.

7. The use of a formulation according to any of claims 1 to 6 as a food supplement.

8. The use according to claim 7, wherein the food supplement is in tablet form.

9. A formulation according to any of claims 1 to 6 or a pharmaceutical preparation thereof for use in medicine.

10. The use of a formulation according to any of claims 1 to 6 or a pharmaceutical preparation thereof in the manufacture of a medicament for administration to male subjects for the improvement of sperm health and maintenance of sperm count levels.

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Patents Act 1977
Examiner's report to the Comptroller under Section 17
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Relevant Technical Fields

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Search Examiner
MR S J PILLING

Date of completion of Search
14 AUGUST 1995

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE: WPI, CAS ONLINE, MEDICINE

Documents considered relevant following a search in respect of Claims :-
1 to 10

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
X	GB 916659	(COLIN) page 1 lines 8 to 15, page 5 lines 19 to 45	1, 7
E,X	EP 0596717 A1	(CHANDRA) page 1 lines 1 to 4 and Example 1	1, 7, 9
X	EP 0564804 A1	(CLINTEC) page 2 lines 34 to 35 and the Example (page 5)	1, 7, 9
E,X	WO 95/00130 A1	(HOWARD) page 1 lines 1 to 18, Examples 4 and 9	1, 7, 9
E,X	WO 94/14458 A1	(ABBOTT) page 1 lines 4 to 8, table 1 (pages 27 to 28)	1, 7, 9
E,X	WO 94/13265 A1	(SMITH) page 1 lines 3 to 9, Examples 10 and 11	1, 9
X	WO 92/21368 A1	(LIFE SCIENCES) page 1 lines 2 to 9, table 2 (page 8) and Claim 2	1, 2
X	CAS PLUS ONLINE Abstract Accession Number 1994:491769 & CZ 278105 (MULLER) 11 August 1993 (see abstract)		1, 7, 9
X	CAS PLUS ONLINE Abstract Accession Number 1994:686683 & CZ 278116 (MULLER) 11 August 1993 (see abstract)		1, 7
X	CH 657967 A (STRONHEIM) 15 October 1986 and see also WPI Abstract Accession Number 86-298776/46		1, 4 to 9

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).